Children Are Not Just Small Adults

Choosing AEDs in Children

Natrujee Wiwattanadittakun, MD

Neurology division, Department of Pediatrics,
Chiang Mai University Hospital, Chiang Mai University

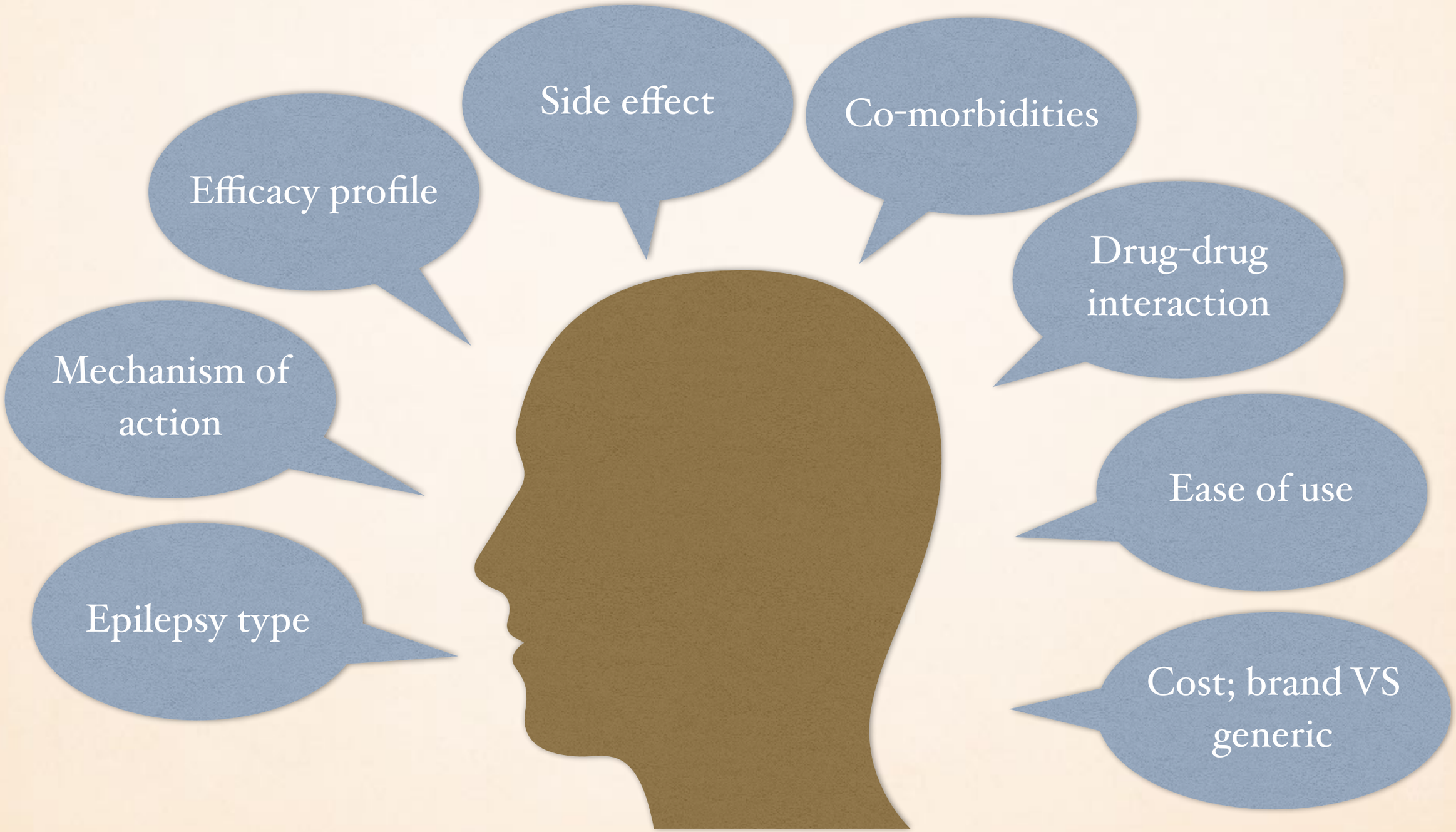
20th July, 2018

Treatment Goals

- Seizure freedom
- No adverse side effects
- Monotherapy
- Easy regimen to follow

Wyllie E. The Treatment of Epilepsy:
Principles and Practice. 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2015.

AEDs Selection



Special Consideration in Children

- Decision to treat —> Accurate Diagnosis !
- Febrile seizure ?
- Think Epilepsy Syndrome
- Contraindication/safety profile
- Etiology: presumptive metabolic disease, genetic
- Specific seizure type

First unprovoked seizure

- Pediatric data
  - 70% of recurrences were within 6 months of the first seizure, 77% by 1 year, and 90% by 2 years
  - Recurrent rates were higher in children with abnormal neurological examination, focal spikes on EEG, and complex partial seizures
  - Recommendation: No treatment until second seizure; > 50% will never have another seizure again

Camfield PR, Neurology 1985;35:1657-1660.

Think epilepsy syndrome
Not just seizure type !

- Some drugs have superior efficacy and others drugs worsen seizure control

- If you know the epilepsy syndrome you can

  - Predict long-term prognosis of childhood onset epilepsy

    - Pharmacoresponsive

    - Remits or require life-long therapy

Epilepsia, 54(3):551–563, 2013
doi: 10.1111/epi.12074

SPECIAL REPORT

Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

***Tracy Glauser, †Elinor Ben-Menachem, ‡Blaise Bourgeois, §Avital Cnaan, ¶Carlos Guerreiro, #Reetta Kälviäinen, **Richard Mattson, ††Jacqueline A. French, ‡‡Emilio Perucca, §§Torbjorn Tomson for the ILAE Subcommission on AED Guidelines**

***Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio, U.S.A.; †Institution for Clinical Neuroscience, Sahlgrenska Academy, University of Göteborg, Göteborg, Sweden; ‡Department of Neurology, The Children's Hospital and Harvard Medical School, Boston, Massachusetts, U.S.A.; §Division of Biostatistics and Study Methodology, Center for Translational Science, Children's National Medical Center, Washington, District of Columbia, U.S.A.; ¶Department of Neurology, University of Campinas (UNICAMP), Hospital das Clínicas, Campinas, Sao Paulo, Brazil; #Department of Neurology, Kuopio Epilepsy Center, Kuopio University Hospital, Kuopio, Finland; **Department of Neurology, Yale University School of Medicine, Yale New Haven Hospital, New Haven, Connecticut, U.S.A.; ††Comprehensive Epilepsy Center, New York University Langone Medical Center, New York, New York, U.S.A.; ‡‡Clinical Pharmacology Unit, Institute of Neurology, IRCCS C. Mondino Foundation, University of Pavia, Pavia, Italy; and §§Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden**

Efficacy Profile

Seizure Type	Class I studies	Class II studies	Class III studies	Level of efficacy for initial monotherapy
Adults with partial-onset seizure	4	1	34	Level A: CBZ, LEV, PHT, ZNS Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB Level D: CZP, PRM
Children with partial-onset seizures	1	0	19	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS

Glauser T et al. Update ILAE evidence. Epilepsia 2013.54;3 :551–563.

Efficacy Profile

Seizure Type	Class I studies	Class II studies	Class III studies	Level of efficacy for initial monotherapy
Adults with generalized onset tonic–clonic seizures	0	0	27	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP. LEV, VGB
Children with generalized onset tonic–clonic seizures	0	0	14	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC

Glauser T et al. Update ILAE evidence. Epilepsia 2013.54;3 :551–563.

Children with Absence Seizure

- Level A: Ethosuximide, valproate
- Level C: Lamotrigine (1 Class I, 7 Class III studies)
- Others: clobazam, clonazepam, leveliracetam, topiramate, zonisamide, gabapentin
- Consider: Teenage girl, side effect

Glauser T et al. Update ILAE evidence. Epilepsia 2013.54;3 :551–563.

Benign Epilepsy with Centrotemporal spikes (BECTs)

- Level C: carbamazepine, valproate
- Level D: Gabapentin, levetiracetam, oxcarbamazepine, STM (3 Class III studies)
- Most of them may not need AEDs (infrequent, nocturnal seizures, onset close to the age of remission)
- Carbamazepine may aggravate new type of seizure/continuous spike-waves during slow wave sleep

Glauser T et al. Update ILAE evidence. Epilepsia 2013.54;3 :551–563.

Juvenile Myoclonic Epilepsy (JME)

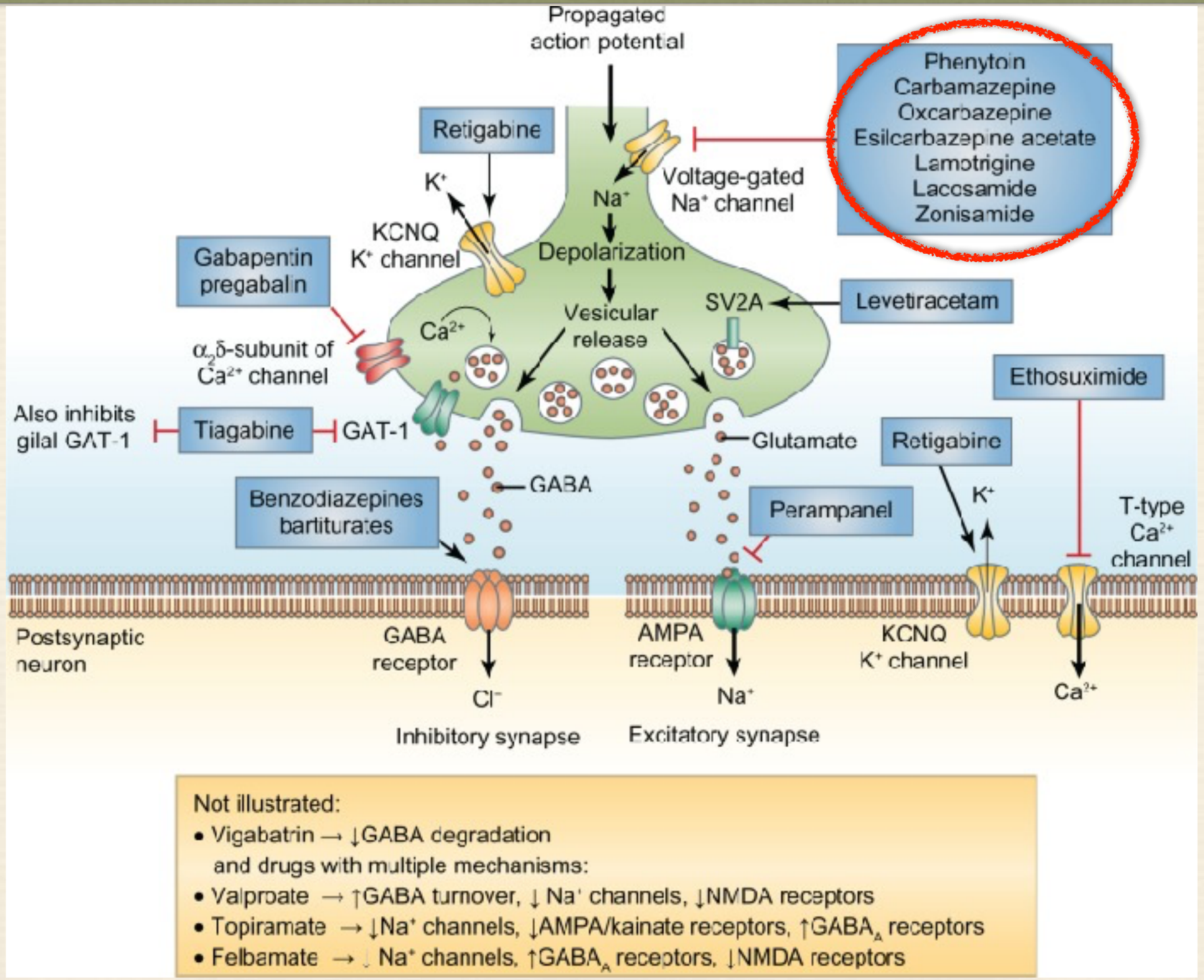
- Level D: Topiramate, valproate (1 Class III studies)
- Others: levetiracetam, zonisamide, lamotrigine, clobazam, clonazepam

Glauser T et al. Update ILAE evidence. Epilepsia 2013.54;3 :551–563.

Efficacy

- Some drugs worsen seizure control
  - Carbamazepine: absence seizure
  - Phenytoin may worsen myoclonic seizure

Mechanism Of Action



Not illustrated:

- Vigabatrin → ↓GABA degradation
  and drugs with multiple mechanisms:
- Valproate → ↑GABA turnover, ↓ Na^+ channels, ↓NMDA receptors
- Topiramate → ↓Na^+ channels, ↓AMPA/kainate receptors, ↑$GABA_A$ receptors
- Felbamate → ↓ Na^+ channels, ↑$GABA_A$ receptors, ↓NMDA receptors

Dravet syndrome

- Severe myoclonic epilepsy of infancy
- Normal infant
- Seizure one less than 1 year old
- Febrile status epilepticus: GTCs, hemiclonic
- Later afebrile seizure; myoclonic, tonic, atypical absence
- Developmental regression/plateu

Epileptic syndrome 5th edition. Chapter 11. 125-156.

Dravet syndrome

- 80% due to **SCN1A mutation**; sodium channel called NaV1.1
- EEG: First year normal, 2-5 years: generalized spikes/ polyspike, multifocal
- Drug of choices: valproate, topiramate, clobazam
- **Avoid: Sodium channel blocker ***** phenytoin, carbamazepine, lamotrigine, vigibatrin**

Epileptic syndrome/Glauser T et al. Update ILAE evidence. Epilepsia 2013.54;3 :551–563.

Adverse Effects

- All antiepileptic drugs; drowsiness, dizziness, and rash; drugs act on the GABA system tend to be more sedating

- Cognitive disturbance: phenobarbital, topiramate, carbamazepine

- Phenytoin-induced gingival hyperplasia increased in children and poorer oral hygiene

Casetta I. Neuroepidemiology 1997;16;296-303.

Serious Adverse Effects

- Valproate-induced fatal hepatotoxicity
  - Young age
    - Age 21-40 years 1:31000
    - Age < 2 years 1:600 ****
- Polytherapy

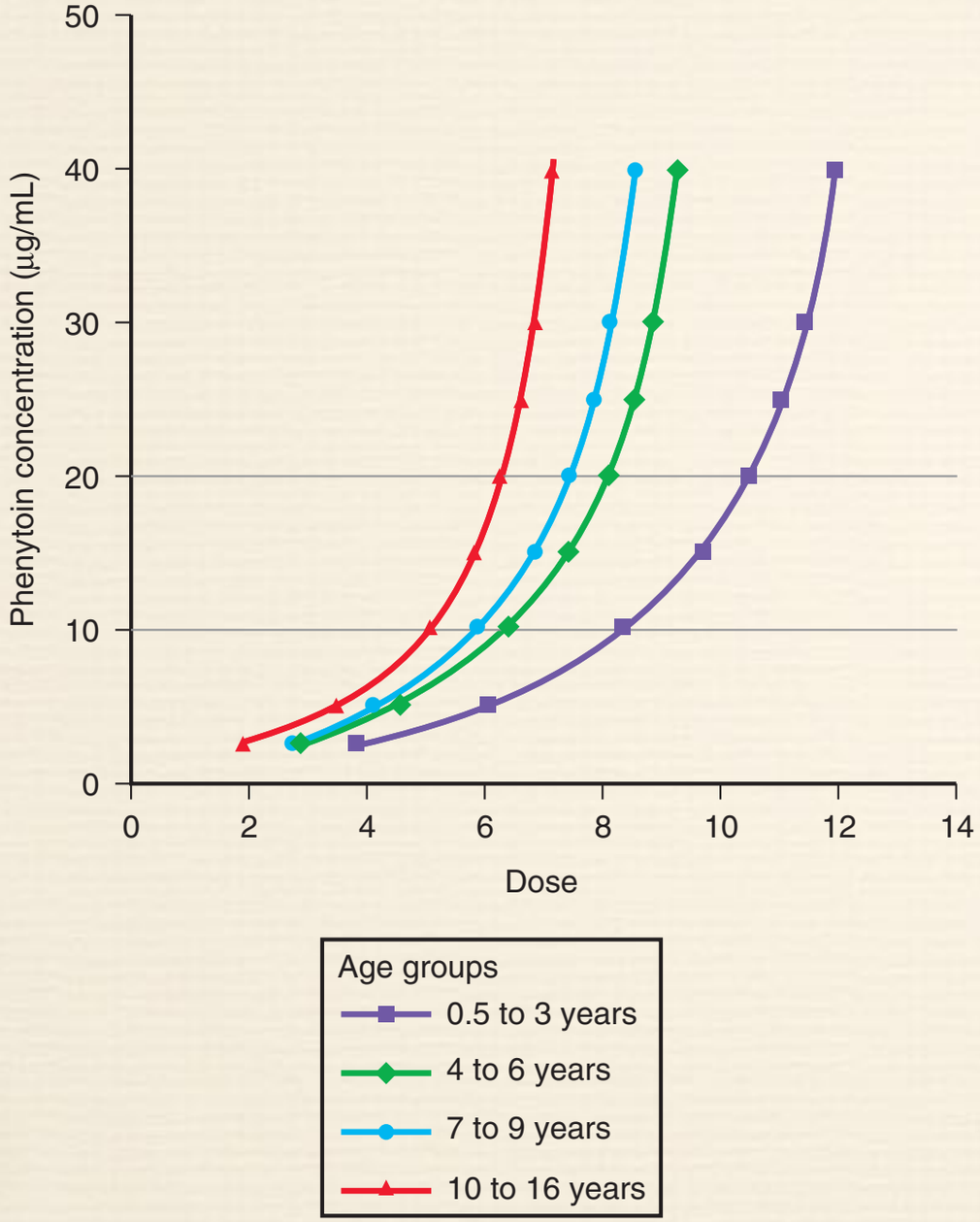
Bryant and Fritz. Neurology 1996;46;465-469.

Pharmacokinetic Fun Facts

- Absorption
  - Phenytoin: Age-dependent: Less than 3 months old poor absorption/unpredictable and may not reliable until 5 years old
- Distribution
  - Phenytoin: V_d declined with age

Matsukura M, Dev Phamaco There 1984;7;160-8.

Pharmacokinetic Fun Facts



Age	Maintenance (mg/kg/day)
Neonate	4-6
0.25-3 years	6-10
4-6 years	5-7
7-9 years	4-7
> 10 years	4-6

Swainman's Pediatr Neurol edition 5th . Chapter 59:811-835

Pharmacokinetic Fun Facts

- Elimination
  - Renal elimination of drugs and metabolite lower than adult until 6 months old
- Metabolism/drug clearance faster than adult; required more frequent dosage
  - Phenytoin : half life 5-14 hours in children ; require two divided dose
  - Carbamazepine : : half life 5-27 hours in children require three divided dose

Bryant and Fritz. Neurology 1996;46;465-469.
Fenichel's Clin Pediatric Neurology 2013; 36-42.

Drug Disposition at Difference Age

	Neonate	Infants, Children	Adolescent
Absorption	↓	↑	A
Plasma protein binding	↓	↓	↓ → A
Metabolism	↓	↑	↓ → A
Excretion	↓	A	A

A = Adult level

Swainman's Pediatr Neurol edition 5th . Chapter 59 :811-835

Ease of Use

- IV VS oral: PHT, PB, VPA, LEV, LCM
- Quick-up titration: phenytoin, phenobarbital, valproate, levetiracetam, zonisamide, lacosamide
  - Not: CBZ, lamotrigine
- Tablet/solution/sprinkles

Tablet

- Crush oral solids form/disguise the taste with a small volume of flavoured drink or food

  - Be aware some drugs lose their properties

- Extemporaneous preparation (small dose)

  - Are you sure about stability, amount of the drug and bioavailability?

Don’t forget

- Caregivers should be thoroughly educated
  - Drug administration technique
  - Who/how/how many times
  - Adverse effect/drug allergy